Triplet 1,4-biradical intermediates in the photocycloaddition reactions of enones and N-acylindoles with alkenes
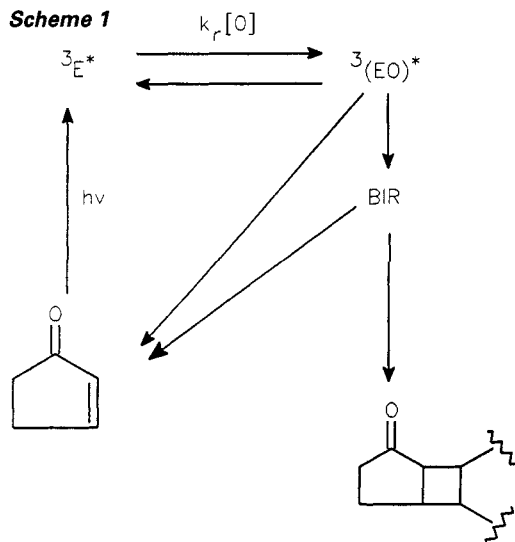
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ABSTRACT The structures, lifetimes, pathways for decay, and rate constants for formation and reaction of the triplet 1,4-biradicals produced as intermediates in the reaction of the triplet excited states of 2-cyclopentenone and of N-acylindoles with alkenes to produce cyclobutane adducts have been investigated. For the photochemical reaction of cyclopentenone with methoxy- and alkyl-substituted alkenes it is concluded that the biradicals are formed by bonding of both the α and the β positions of the enone to the less substituted end of the alkene. It is also concluded that the regiochemistry and stereochemistry of the products of the reaction are determined by the outcome of the competition between reversion to starting material and closure to product for each of the various intermediate biradicals which lead to each of the reaction products. This implies that the long held triplet exciplex theory used to rationalise the reaction regiochemistry is incorrect. Evidence is also presented which suggests that while the same may be true for the photocycloaddition of acrylonitrile with cyclopentenone, this reaction may also be proceeding from the singlet excited state of the enone. For the photochemical reaction of N-acylindoles with alkenes it is concluded that the reaction regiochemistry is determined by preferential formation of the biradical derived from bonding between the 2-position of the indole and the less substituted end of the alkene.

INTRODUCTION Beginning in the early 1960's with the work of de Mayo,[1] Eaton[2] and Corey,[3] and continuing up to the present day[4,5] numerous groups have explored synthetic applications and conducted mechanistic investigations of the photochemical cycloaddition reaction between alkenes and cyclopentenones and cyclohexeno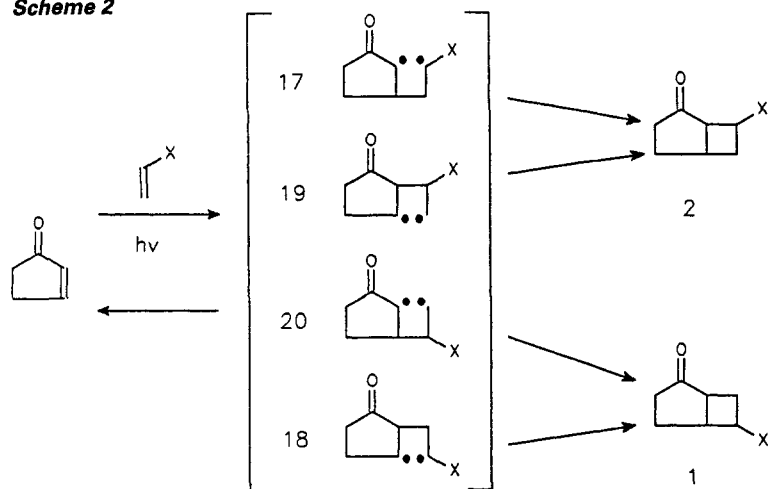nes to yield cyclobutane adducts. The mechanistic model commonly used to plan or interpret these reactions is shown in scheme 1. Excitation and efficient intersystem crossing yields the triplet excited state of the enone E which interacts with the alkene O to produce a triplet exciplex $^3(EO)^*$. Decay of the exciplex produces biradical BIR which partitions between the starting materials and the product.

The exciplex was introduced as an intermediate in order to explain what was perceived to be an inordinately large rate constant for addition of the triplet enone to the alkene, which can be estimated to be several orders of magnitude faster than the rate of addition of free radicals to alkenes. In addition, the exciplex was used to rationalise the reaction regiochemistry; polar, electron rich alkenes selectively yield the head-to-tail isomer **1** (scheme 2), while early work suggested that

Scheme 1

$$^3E^* \underset{}{\overset{k_r[O]}{\rightleftarrows}} {}^3(EO)^*$$

electron poor alkenes preferentially produce the head-to-head product **2**. This selectivity was nicely explained by an electrostatically directed orientation in the exciplex of the alkene dipole with that of the enone triplet, which was assumed to be inverted from that of the ground state. Recent work has cast doubt on this explanation. For example, both electron rich and electron poor alkenes have been found by flash photolysis to quench the triplet excited state of the enone with similar rates, which would not be expected for formation of an excited state charge transfer complex.[6] In addition, it has recently been found that electron poor alkenes do not always yield the head-to-head regioisomer preferentially.[7]

The intermediacy of a biradical intermediate as shown in scheme 1 is uncontroversial, partly because of the triplet multiplicity of the reaction which, in the absence of a pathway for rapid spin inversion, normally precludes a concerted cycloaddition mechanism. In addition, Schenk isomerisation of the alkene reaction partner is observable, and any alkene stereochemistry is lost in the product. Furthermore, products of disproportionation of the intermediate biradicals are isolated in many reactions. However, little information about the structures of the intermediate biradicals or their lifetimes and modes of decay is available. For example, in the reaction of cyclopentenone with a mono-substituted alkene (scheme 2) four biradicals are possible, derived from bonding of either end of the alkene to either the α or the β position of the enone. Chemical intuition would suggest that the primary radical containing biradicals would be unimportant, but there are conflicting views on which position of the enone is involved in initial bonding.[8] The normally effective technique of flash photolysis is not useful here since the biradicals have lifetimes which, as we shall show below, are similar to that of the enone triplet excited state. In addition, flash photolysis cannot easily distinguish between the different biradical structures. Virtually nothing is known about the relative amounts formed of each of the biradicals shown, nor about how efficiently each of them proceeds to the cyclobutane products rather than reverting to the starting materials.

Scheme 2

Our interests in the synthetic and mechanistic aspects of the photochemical deconjugation reactions of acyclic enones[9] and cyclic enones[10] and in the application of photocycloaddition of enones with alkenes to the synthesis of natural products[11] have led us to turn our attention to the problem of the mechanism of the photocycloaddition reaction between cyclic enones and alkenes. We have studied the question of whether the initial bond between the alkene and the enone in the intermediate biradical is to the α or the β-position of the enone and whether it is to the more or less substituted end of the alkene. We have also used radical rearrangement reactions to clock the lifetimes and yield information about the structures of the intermediate biradicals. By using hydrogen selenide as a radical trap we have reduced the 1,4-biradicals generated in the reaction and hence obtained information about their structures and relative rates of formation. Combination of this data with data for the quantum yield of formation of photoadducts has allowed us to estimate to what degree each of the intermediate biradicals proceeds to products rather than reverts to starting material. The question of how the intermediate biradicals partition has also been probed by generating the biradicals by an alternative route. A summary of this work, much of which has not yet been published, is presented here. In addition, the results of a similar study of the photochemical cycloaddition reaction of alkenes with N-acylindoles, which proceeds by a similar mechanism, are also described here.

Photocycloaddition of cyclopentenone with vinylcyclopropane

We have found[12] that ultra-violet light irradiation of benzene solutions of cyclopentenone containing vinylcyclopropane yields stereoisomers of the cyclobutane containing adducts **3** and **4** along with similar quantities of the geometrical isomers of the cyclopentenone adducts **5** and **6**. The cycloadducts **3** and **4** are the products of closure of the expected biradicals **7-10**, although the primary radical containing biradicals **9** and **10** are anticipated to be less important, as will be confirmed below. The adducts **5** and **6** are apparently derived from intramolecular disproportionation of the rearranged biradicals **11** and **12** which arise from opening of the cyclopropyl alkyl radical present in **7** and **8**. The rate of the opening of a cyclopropyl alkyl radical to a homoallylic radical is known[13] to be *circa* 2×10^7 s^{-1}; since cycloadducts **3** and **4** are formed from biradicals **7** and **8** competitively with, and in similar amounts to adducts **5** and **6**, the lifetime of the biradicals **7** and **8** can be estimated to be of the order of 50 ns. In addition, since **5** and **6** are formed in comparable quantities to each other as well as to **3** and **4**, it can be concluded that the biradical intermediates formed in the photocycloaddition reaction of cyclopentenone with this vinylcyclopropane are formed by bonding to both the α and the β positions of the enone.
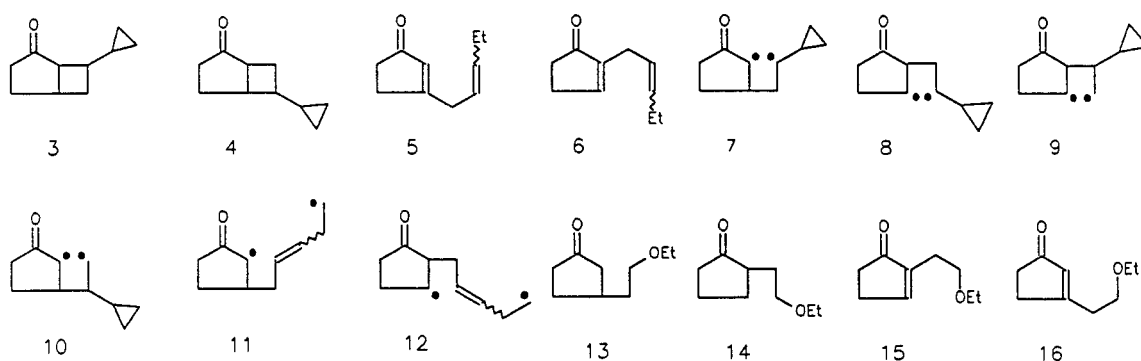
Photochemical cycloaddition of cyclopentenone with *cis* and *trans* 2-butene, 2-methylpropene and ethyl vinyl ether, and trapping of the 1,4-biradical intermediates with hydrogen selenide

Ultra-violet light irradiation of benzene solutions of 2-cyclopentenone containing ethyl vinyl ether yields stereoisomers of the head-to-head and head-to-tail cycloadducts **2** and **1** (scheme 2; X = OEt), respectively.[14] We have repeated this reaction and determined the regioisomeric ratio **2:1** to be 1.0:3.1.[15] We have also found[15] that when the reaction is performed with hydrogen selenide present in the solution cycloadduct formation is completely suppressed and the products formed instead are **13-16** in the ratio 5.7:3.2:3.5:1.0, respectively. Products **13** and **14** are consistent with reduction (by hydrogen atom transfer from hydrogen selenide) of the non-primary radical containing biradicals shown as intermediates **17** and **18** (X = OEt) in scheme 2. Products **15** and **16** are consistent with disproportionation of the partially trapped biradicals with hydrogen selenyl radical. The absence of products of trapping of the primary radical containing biradicals **19** and **20** (X = OEt) shown in scheme 2, combined with the absence of cycloadducts when hydrogen selenide is present, suggests that such biradicals are not formed as intermediates in the photocycloaddition reaction; this supports the assumption made above that primary radical containing biradicals such as **9** and **10** are not formed in the reaction of triplet cyclopentenone with vinylcyclopropane. It can be argued that species such as **13** and **14** could be formed by direct photoreduction of the cyclopentenone excited state by hydrogen selenide followed by coupling of the resultant radical with the alkene; however, this can be rejected since the rate constants for alkene-radical coupling reactions[16] are *circa* six orders of magnitude slower than the rate constants for interception of radicals by hydrogen selenide.[17] Thus direct photoreduction of excited cyclopentenone would be expected to yield cyclopentanone (which, in fact, is an observed product) and not products **13-16**.

The relative amounts of **13-16** isolated can be used to calculate the relative amounts of the two 1,4-biradicals **17** and **18** produced and hence their relative rates of formation. This calculation

indicates that the biradical leading to the head-to-head cycloadduct **2** (X=OEt) is formed at the same rate as the biradical leading to the head-to-tail cycloadduct **1** (X=OEt) and confirms that the biradicals are produced by bonding of the alkene to both the α and the β positions of the enone. Since the cycloadduct **1** is the major regioisomer produced in the absence of hydrogen selenide it can be concluded that the reaction regiochemistry is determined by the extent to which each of the intermediate biradicals reverts to starting materials in competition with closure to the products.

Similar results have been obtained with 2-methylpropene as the alkene partner. In the absence of hydrogen selenide the products are cycloadducts **21** and **22**, and adducts **23** and **24**. These are formed in the ratio 69.5:18.6:2.9:9.1, respectively. The biradicals responsible for the formation of these products are shown in scheme 3; thus **23** is derived from intramolecular disproportionation of **25** which is also a precursor of **21**, and **24** is derived from intramolecular dis-

Scheme 3

proportionation of **26** which is also a precursor of **22**. Combination of the relative yields of **21** and **23** and those of **22** and **24** gives a measure of the reaction regioselectivity and indicates a head-to-head:head-to-tail ratio of 27.7:72.4. When the reaction was performed in the presence of hydrogen selenide no adduct formation was observed and the products **29-34** were obtained instead in the ratio 0.4:2.3:15.0:10.0:64.5:7.5.
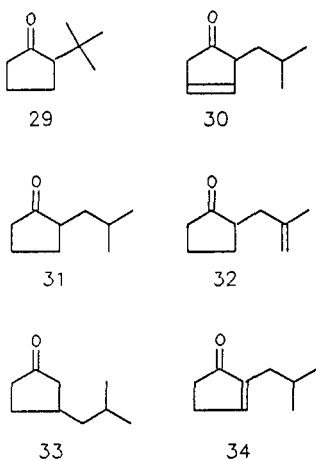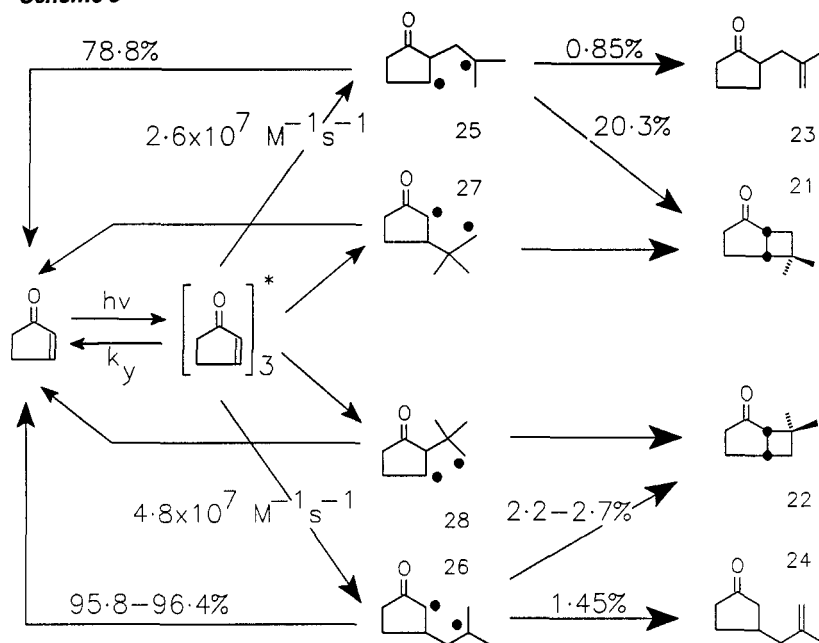

Formation of products **31** and **33** is consistent with complete reduction by hydrogen selenide of biradicals **25** and **26**, respectively, while formation of **30, 32** and **34** is consistent with partial reduction of **25** and disproportionation of the resulting radical with hydrogen selenyl radical. The isolation of these products, along with the formation of only trace amounts of **29** (derived from reduction of **28**) and the absence of products of trapping of **27** further demonstrates that triplet excited cyclopentenone reacts with alkenes by bonding of both the α and the β positions of the enone to the less substituted end of the alkene. Comparison of the combined relative yields of **30-32** and **34** with that of **33** indicates that the biradicals **25** and **26** are formed in a ratio of 35:65, respectively. Comparison of this with the ratio of (**23**+**21**):(**22**+**24**) indicates that the reaction regiochemistry is determined *not* by the relative rates of formation of the biradicals (which would be expected if the regiochemistry were controlled by orientation in an exciplex) but rather by the degree to which they revert to starting materials rather than proceed to products.

For each of the products **21-24** shown in scheme 3 an expression relating the quantum yield of product formation to the rate constants for formation and decay of the biradicals **25-28** can be derived which is a function of the 2-methylpropene concentration and the triplet excited state

lifetime of the enone. We have measured these quantum yields over a wide range of alkene concentration. Assuming a triplet enone lifetime of 22ns[18] and assuming that the yields of **30-34** correctly represent the relative rates of formation of biradicals **25** and **26**, the data can be used to calculate the rate constants for formation of **25** and **26** and the proportions of each which proceed to products or revert to starting materials. The results are summarised in scheme 3.

Scheme 4
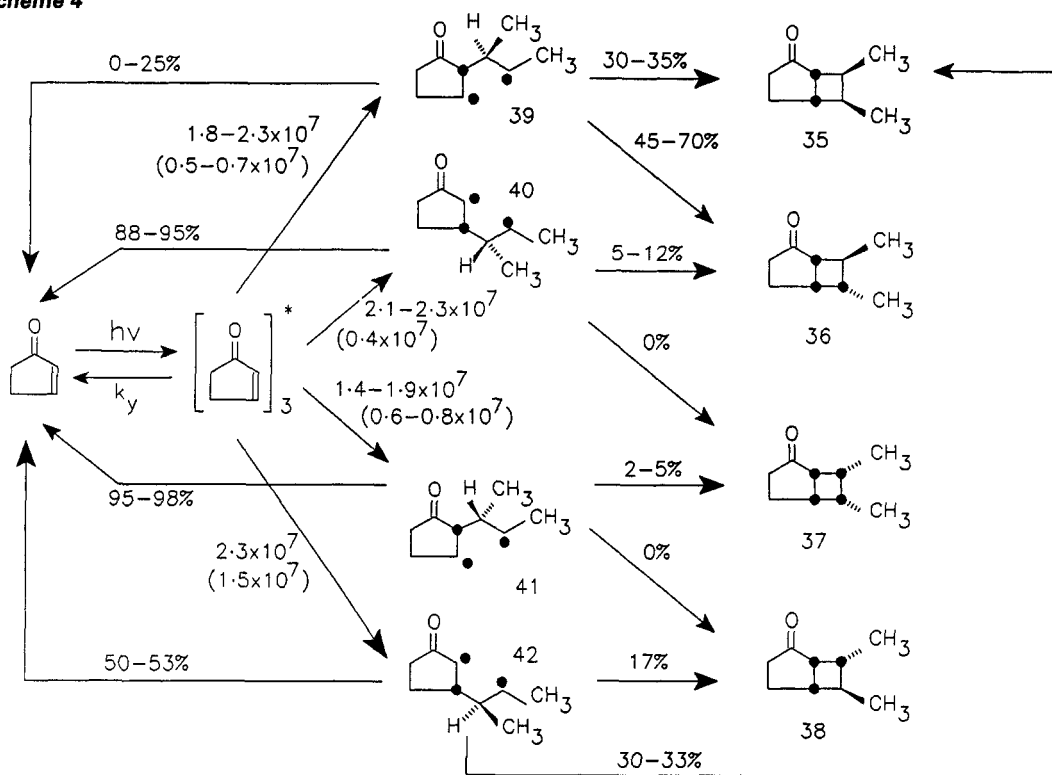
The same procedure has been applied to the photochemical reaction of 2-cyclopentenone with cis-2-butene and with trans-2-butene. The cycloadducts **35-38** are formed in the ratio 42.6:43.5:2.2:11.7 with cis-2-butene, and in the ratio 50.2:28.5:2.1:19.2 when trans-2-butene is used. The product ratios were determined at low conversions so that geometrical isomerisation of the alkene by the Schenk mechanism is negligible. In the presence of hydrogen selenide adduct formation was inhibited completely and the products of trapping of the intermediate biradicals **39-42** were obtained instead. These possessed structures **43-51**. The relative yields of **43-51** obtained when cis-2-butene was used as the alkene were, respectively, 2.3:2.0:2.0:13.2:12.6:10.3:27.7:27.7. With trans-2-butene the ratio was 1.4:2.4:1.2:2.4:9.1:14.0:10.2:47.6:12. These data allow the relative yields of the biradicals **39-42** to be estimated, although a small degree of uncertainty arises because stereochemical information about the biradicals is lost in the trapped adduct **49**. Combination of this data with those for the quantum yield
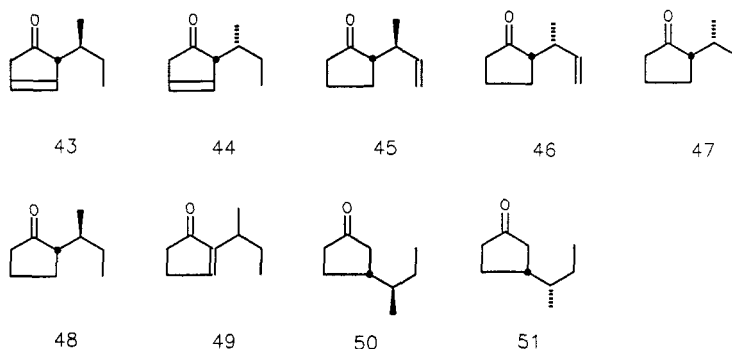
of formation of each of the adducts **35-38** at various concentrations of *cis* and *trans*-2-butene and assuming a 22ns triplet enone lifetime allows estimation of the rate constants for formation of the biradicals **39-42** and the proportions of each which proceed to products or revert to starting materials. The results are shown in scheme 4. The rate constants over the reaction arrows are in units of $M^{-1}s^{-1}$ and those in parentheses refer to *trans*-2-butene while those outside the parentheses refer to the *cis* isomer. The ranges shown for some of the rate constants in the scheme reflect the ambiguity introduced by the loss of stereochemical information in **49**.

The results summarised in schemes 3 and 4 represent the first complete characterisation of the triplet 1,4-biradicals implicated in enone-alkene photocycloaddition. More importantly they hint at the factors which govern the extent to which each of the various possible biradicals are formed and the extent to which they revert to starting materials or proceed to products. For example, the initial interaction of the enone and the alkene apparently involves a "skewed" transition state between only **one** end of the alkene (the less substituted end if possible) with either the α or β position of the enone. Thus biradicals **40** and **42** are formed at similar rates from *cis*-2-butene; if addition of the alkene were to proceed by interaction of the excited enone simultaneously with both termini of the alkene then it would be expected that **40** would be formed more slowly, reflecting an *endo* orientation of approach, while **42** would form more rapidly by a less sterically demanding *exo* orientation of approach. The data also suggest that the biradicals do not necessarily close to the more stable cycloadduct; thus the major fate of the biradical **39** is closure to **36** rather than the more stable **35**.

Photocycloaddition reaction of 2-cyclopentenone with acrylonitrile

Ultra-violet light irradiation of a benzene solution of 2-cyclopentenone in the presence of acrylonitrile yields four cycloadducts with the structures **52-55**. Using hydrogen selenide we have been unable to trap the expected triplet 1,4-biradicals **56** and **57**. We have, however, been able to generate these biradicals by an independent route involving sensitised photodecarbonylation of the bicyclic diketones **58** and **59**. The triplet biradicals produced partition to give 2-cyclopentenone and **52-55**. Thus for diketone **58** photolysis yields 2-cyclopentenone and two of the four cycloadducts (i.e. **52** and **53**) in an enone to adduct ratio of 3.7:1, while photolysis of diketone **59** yields 2-cyclopentenone and the other two cycloadducts (i.e. **54** and **55**) in an enone to adduct ratio of 1:1. These two pairs of adducts are produced from photocycloaddition of acrylonitrile with cyclopentenone in the ratio $(52+53):(54+55)=3:4.8$.
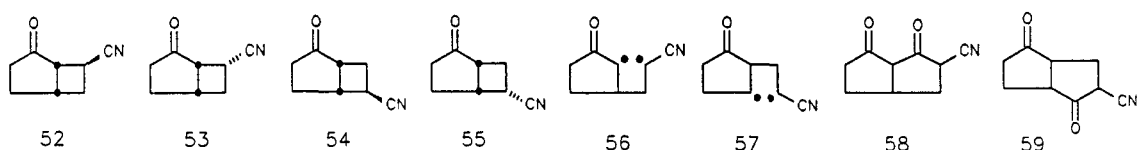

These data lead to two conclusions. Firstly, the photocycloaddition of acrylonitrile with cyclopentenone apparently yields the head-to-tail regioisomers **54** and **55** preferentially. This is in contrast to the original report that 2-cyclohexenone yields photocycloadducts with acrylonitrile with head-to-head regiochemistry, which was partly responsible for the suggestion that a polarised excited state complex controls the reaction regiochemistry.[3] Secondly, the relative amounts of the adducts and enone produced from each of the biradicals **56** and **57** combined with the regioisomeric ratio of adducts obtained from photocycloaddition of cyclopentenone with acrylonitrile suggest that if adducts **52-55** are formed from the enone triplet excited state then biradical **56** is formed 1.5 times faster than biradical **57**, and therefore that as with the other alkenes examined in this work the product regiochemistry is governed by the fates of the biradicals rather than by their relative rates of formation. In fact, our failure to intercept biradicals **56** and **57** with hydrogen selenide, along with the fact that the triplet excited state energy of acrylonitrile has been reported to be *circa* 10 kcal/mol. lower than that of cyclopentenone[19] suggests that the cycloaddition reaction does not proceed from the enone triplet excited state as has long been assumed. We have examined this further and find that the sensitised (xanthone) irradiation of cyclopentenone with acrylonitrile leads to the preferential formation of enone dimers via the enone triplet excited state rather than adducts

52-55. We also find that whereas the quantum yield of enone dimer formation under direct irradiation conditions increases as the enone concentration is increased, the quantum yield of cycloadduct formation with acrylonitrile is *constant* rather than reduced by the increased dimerisation efficiency. One interpretation of these facts is that the formation of adducts **52-55** occurs by interaction of the *singlet* excited state of the enone with the alkene.

Photocycloaddition reactions of alkenes with N-acylindoles

Ultra-violet light irradiation of N-aroylindoles and N-acetylindole in the presence of alkenes leads to cyclobutane formation by addition of the alkene termini to the 2- and 3-positions of the 5-membered ring of the heterocycle.[20,21] We have extended this reaction to other N-acylindoles[22] in which the acyl group is, for example, benzyloxycarbonyl, trimethylsilylethoxycarbonyl, *tert.*-butoxycarbonyl, and cyanoethoxycarbonyl. Use of these derivatives allows the removal of the N-substituent from the cycloadducts under a variety of mild neutral, acidic and basic conditions. We have also examined the mechanism of this reaction.[23-29] We have found that the lowest singlet excited state of N-aroylindoles is a charge transfer state[23,24] and is not involved in cycloaddition. Direct irradiation of N-benzoylindole or N-ethoxycarbonylindole results in photo-Fries rearrangement,[25] and production of 3-benzoylindole or 3-ethoxycarbonylindole, respectively, as the major products. If alkenes are present then they react with the triplet excited state[26] of the indole derivative to form biradicals[27] which either ring close to cycloadducts or revert to ground state starting materials.[27,28] These conclusions are based on the results of quenching studies and the loss stereochemistry of the alkene in the cycloadduct, as well as the observation of Schenk isomerisation of the unreacted alkene (scheme 5).

Scheme 5
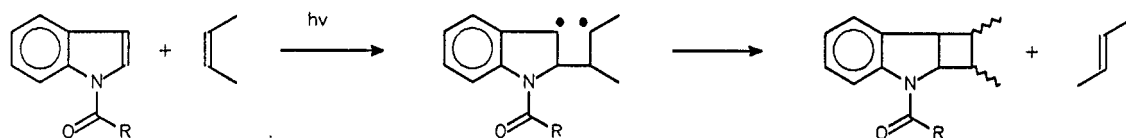
The photocycloaddition reaction with vinylcyclopropane yielded similar results to those obtained from reaction of this alkene with cyclopentenone and leads to the conclusion that the biradical intermediates have triplet lifetimes of the order of 100ns and are formed by selective bonding between 2-position of the indole and the less substituted end of the alkene.[28] This conclusion has been confirmed by trapping of the intermediate biradicals with hydrogen selenide.[29] This result explains the observed propensity of N-acylindoles to yield the "head-to-tail" adduct **60** rather than the "head-to-head" adduct **61**.

60   61   62   63

64   65   66
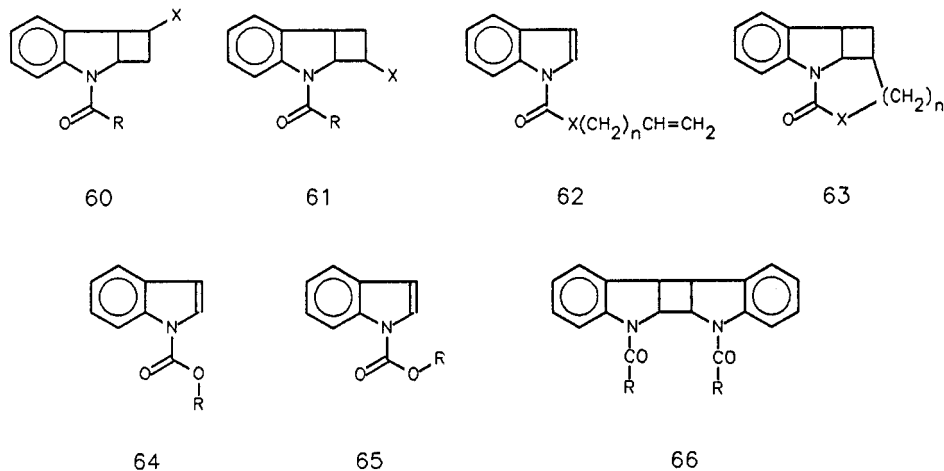
We have successfully reversed this regioselectivity by tethering the alkene to indole as shown in structure **62**. For $X = CH_2$, $n = 0$, 1 or 2, sensitised irradiation of **62** yields **63** in excellent yields. The reaction fails when $X = O$, even though the intramolecular cycloaddition of alkenes still proceeds efficiently. On the basis of the results of molecular mechanics calculations, and from variable temperature NMR evidence we conclude that this is because the urethane linkage is more stable in conformation **64** than **65** and that interchange between these is slow during the triplet excited state lifetime. We have also observed dimerisation of N-acylindoles under sensitised conditions to give **66** ($R = OEt$, OCH_2Ph, $OCHCH_2$). This reaction is common for benzothiophenes and benzofurans but for the indole nucleus has only been seen previously for N,3-diacetylindole.[30]

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